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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,754	KOELSCH ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Claims 1-6 are pending and are before the Office for examination on their merits.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 112 as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application No. 60/141,363; 60/168,060; 60/177,836; fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The above stated applications do not provide the necessary crystallization information necessary to make and or use the invention as claimed in the instant application. Only provisional applications 60/210,292 filed on 08 June 2000 and 60/178,368, filed 27 January 2000 provides support for the instant application that would enable the claimed invention and allow one of ordinary skill in the art to recognize

that Applicants were in possession of the claimed invention. The 60/178,368 application provides the details found in Table 2 as claimed, and 60/210,292 discloses the actual three-dimensional structural coordinates. As such, the effective filing date of the instant application for prior art purposes will be 27 January 2000. The claim of priority benefit for Application(s) Nos: 60/141,363 (6/28/1999); 60/168,060 (11/30/1999); and 60/177,836 (1/25/2000) is denied.

Compliance with Sequence Rules

3. The sequence listing, filed in computer readable form (CRF) and paper copy on 06 February 2004, has been received and entered. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) In Figure 1, amino acid sequences of memapsin-2 polypeptides are disclosed without SEQ ID NO identification.
b) Table 2 is a description of the crystallized memapsin 2 protein, however, there is no indication as to what linear residues of the protein are actually represented in the crystal (e.g. residues 1-488 of SEQ ID No: 2).

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper

copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Specification

4. The abstract of the disclosure is objected to because the Abstract is too long (e.g. exceeds 150 words). Furthermore, the Abstract should be narrowed to a more precise summary directed to the instant invention rather than a running commentary on each step practiced in the invention and speculative uses for the invention. Correction is required. See MPEP § 608.01(b).

5. The disclosure is objected to because of the following informalities: The descriptions under the Brief Description of the Drawings for Figures 6, 7 and 9 (p.8) reference colors to distinguish various features of the drawings. However, the drawings are in black and white and thus the description is not consistent with the actual drawings.

Appropriate correction is required.

Claim Objections

6. Claim 1 is objected to because of the following informalities: OM-99-2 is a general name given by Applicants to SEQ ID No: 28. Claim 1 would be clearer if the SEQ ID No: was included in the claim. Appropriate correction is required.

7. Claim 3 is objected to because of the following informalities: The claim uses the acronym 'APP'. In the first instance of any acronym, the entire reference word should be spelled out in full with the acronym followed in parenthesis. In the instant case, β-amyloid precursor protein (APP) would be proper. Appropriate correction is required.

8. Claim 1 is objected to because of the following informalities: The examiner suggests changing "an K_i" to "a K_i" to reflect more accurate grammar.

9. Claim 6 is objected to because of the following informalities: The claim is drawn to creating a data base of data which is obtained by modeling inhibitors based on the 'crystallization coordinates of memapsin 2...'. This terminology is contrary to art-accepted terminology for the description of proteins three-dimensional structure. "Three-dimensional structural coordinates" is more appropriate than 'crystallization coordinates', while a skilled artisan would likely be able to guess what is meant by the phrase, it is a phrase which nonetheless is not used in the art as it is an inaccurate description. Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 2nd paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to treating a patient to decrease the likelihood or to decrease the progression of AD by administering an inhibitor to an

individual. However, administering the inhibitor to just any random patient will not be effective and therefor administration must be to an 'individual in need thereof'.

12. Claims 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to specific limitations regarding the inhibitor. However, the claims fail to actually provide any method steps for achieving the stated limitations. It is the opinion of the examiner that it appears Applicants are trying to almost claim methods of designing the inhibitors *in silico* without actually doing so. However, by doing this, several areas are left indefinite. For instance, claim 4 states 'The method of claim 1, wherein the inhibitor is modeled using the crystallization coordinates.....'; in claim 1 there are two different and very distinct inhibitors described. One which has a K_i of 10^{-7} M and one which must merely be able to bind to a memapsin 2 crystal. Thus, it is unclear whether or not the *in silico* designed and identified inhibitors of claim 4 must possess both a K_i of 10^{-7}M, and if so, how would one test this....this is strictly and *in vitro* analysis; and also be able to fit to the crystal of memapsin 2 as claimed. Thus, there appears to be several distinct and essential method steps missing in these reach through claims which make the claims unclear and indefinite.

Claim Rejections - 35 USC § 112 – 1st paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the**

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement:

14. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibitors OM-99-1 and OM-99-2 (SEQ ID No: 27 and 28, respectively), does not reasonably provide enablement for any inhibitor that interact with the crystal of memapsin 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The instant claims are drawn to a method of treating a patient or decreasing the likelihood of developing Alzheimer's by administering an inhibitor with a K_i of 10^{-7} M or one that can bind to a crystallized memapsin 2 proteins. A critical aspect of the claimed invention is the necessary reproducibility of the crystallization conditions and making the co-crystal memapsin-2:SEQ ID No: 28 so that a skilled artisan can make and use the invention as claimed. However, in the absence of the actual exact protein content used to make the crystals and absence the actual structural coordinates used to model inhibitors, the instant claims would require undue experimentation by a skilled artisan in order to determine any inhibitors other than OM-99-2 and OM-99-1 that might be useful in the treatment of Alzheimer's and those which meet the limitations of the claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

On pages 45-47 the instant specification discloses a how to make the memapsin 2 recombinant protein and pages 47-50 describe conditions to co-crystallize mempasin with SEQ ID No: 28 (OM-99-2). The space group and unit cell dimensions of the crystals produced are disclosed in the instant Table 2. However, the amino acid sequence used to make the protein crystals is unclear because the specification does not disclose this information. Furthermore, there are no atomic coordinates disclosed in the specification so a skilled artisan could not even attempt to guess as to what part of the protein was actually crystallized. However, even if the atomic coordinates were disclosed, this is not a reliable way to indicate the protein content of a crystal because information about the polypeptide sequence may only be available for those parts of the

polypeptide that are well-ordered in the crystal and actually visible; those parts which are highly disordered can not be modeled and will be absent or modeled simply as alanines or glycines. The presence or absence of any residue of a protein can be of critical importantance for the preparation of the crystallization sample (see below) leading to successful crystallization.

While the prior art and the specification provide guidance on how to make memapsin 2 polypeptide crystals (see pages 47-50), this guidance is insufficient to produce the particular crystals encompassed by the scope of the claims. In order to make protein crystals, the following must be clear: the preparation and chemical composition of the molecules to be crystallized and the crystallization conditions, including the type and amount of reagents used and the type of methods employed. While the instant specification describes the cloning and purification of the memapsin 2 protein, these methods do not enable one of skill in the art to make crystals of memapsin 2 that are within the scope of the claims. Crystallization experiments must be done in order to determine if a polypeptide will crystallize, and X-ray structure determination experiments must be done in order to determine if the polypeptide is encompassed by the scope of the claims. The guidance found in the specification for crystallization conditions (i.e. range of precipitant used, i.e. types of heavy metals/heavy metal compounds, range of temperature) is too broad and incomplete to be useful. Small changes in any of the aforementioned factors (i.e. polypeptide composition and crystallization conditions) can change the unit cell dimensions and space group symmetry of a crystal dramatically or even prevent crystals from forming (see Ollis et al.

pp. 647-650); therefore, precise instruction about how to make protein crystals is required so that undue experimentation is not required. Due to the unpredictable nature of the art, specific information on how to make each crystal encompassed by the scope of the claims is required for enablement. One of skill in the art would be unable to predict how to make any members of the genus encompassed by the scope the claims; to do so would require undue experimentation.

Therefore, the instant claims are not enabled for their full scope without disclosure of the exact amino acid/polypeptide composition used to create the memapsin 2 protein crystals and the atomic structure information for which the inhibitors are designed around and only OM-99-2 and OM-99-1 appear to fulfill the claimed inhibitor limitations.

15. Claims 4-6 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease by administering an effective amount of an inhibitor of memapsin 2 with a particular K_i or which binds to crystallized memapsin 2 with the parameters of Table 2 (claim 1), wherein the inhibitor is modeled using a computer program based on the three-dimensional structural coordinates of memapsin 2 (claim 4) and specifically those found in Table 2 (claims 5 and 6). However, Table 2 is merely a table which possesses X-ray data collection

statistics and no structural information is present in said Table or the rest of the instant application. As such a skilled artisan would not be able to graphically display the memapsin 2 structure let alone model any inhibitors based on its structure without the burden of undue experimentation.

Factors to be considered in determining whether undue experimentation is required are above. MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

Precedence has been established for lack of enablement for missing essential matter because a claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling according *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). See also MPEP § 2164.08(c). Such essential matter may include missing elements, steps or necessary structural cooperative relationships of elements described by the applicant(s) as necessary to practice the invention. In the instant case, the claim is directed to Table 2 in the specification. The specification

describes using the structure of memapsin 2 with known computer programs that can model inhibitor/protein interactions in a rational drug design approach (see pp. 22-23). However, it is vital and necessary to have the structural coordinates in order to practice this part of the invention and this is stated in the first sentence which states that the approach to designing inhibitors combined structural information and computer modeling (see p. 22, lines 3-10). Clearly, there are no three-dimensional structural coordinates disclosed in the instant application (or its parent) and as such one skilled in the art would not be able to practice the invention without the undue burden of solving the memapsin 2 crystal structure themselves, which is non-trivial at best.

The enablement requirement is clearly predicated upon not imposing undue experimentation upon a skilled artisan. In the absence of any sort of disclosure of the three-dimensional structural coordinates, a skilled artisan would necessarily be required to isolate the gene and over express the protein in a suitable host, purify the protein to homogeneity, crystallize the protein, isolate the crystal, collect X-ray data from said crystal, solve the three-dimensional structure and refine the data so as to have a good working model of memapsin 2; and all of this just to get to the starting point of practicing the claimed invention; all of which is not seen as undue.

Written Description:

16. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one

skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus: *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

As stated *supra* the claims are drawn to methods of decreasing the likelihood or decreasing the progression of Alzheimer's by administering an inhibitor in an effective amount to an individual. The specification describes the crystallization, expression and use of a protein, memapsin 2, which is thought to be linked to the production of protein plaques/tangles in the brains Alzheimer's sufferers. The specification adequately describes the design of two inhibitors of this protein, OM-99-1 and OM-99-2, SEQ ID Nos: 27 and 28, respectively. However, nowhere in the specification have these

inhibitors, or any others, actually been tested *in vivo* on anything. Thus, possession in this case comes down to potential false prophecies because the two species of inhibitors that are described in the specification may not even work to decrease the progression or the likelihood of developing the disease and Applicants are not in possession of any sort of genus of inhibitors, to which the claims are drawn, that will also work. Furthermore, there is no correlation between the limitations that the inhibitors of memapsin 2 must have K_i's of less than 10^{-7} or those that will bind the crystallized enzyme mempsin 2 with that of a successful inhibitor which decreases the progression or likelihood of developing Alzheimer's. Consequently, there is no structure function relationship that links the claimed inhibitors to the successful achievement of decreasing the progression or likelihood of developing Alzheimer's.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

17. Claims 4-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was

not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are directed to methods of treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease by administering an effective amount of an inhibitor of memapsin 2 with a particular K_i or which binds to crystallized memapsin 2 with the parameters of Table 2 (claim 1), wherein the inhibitor is modeled using a computer program based on the three-dimensional structural coordinates of memapsin 2 (claim 4) and specifically those found in Table 2 (claims 5 and 6). However, Table 2 is merely a table which possesses X-ray data collection statistics, such as, resolution range for diffraction of the crystal, unit cell parameters and the predicted space group (data statistics) and refinement parameters, such as, the % error in a model as defined by $R_{working}$ and the independent data group of R_{free}, the average temperature factors (B-factors as stated in $Å^2$, etc.). The information in Table 2 are standard statistics for data and refinement analysis but in no way reflect any structural coordinates of memapsin 2 and thus, there is no disclosure of any three-dimensional arrangement of atoms as claimed. Coordinates for any three-dimensional structure are arranged in a Cartesian coordinate system where each atom (except hydrogen atoms) are spatially defined in an x, y, z position and this type of information for disclosing the structural coordinates is essential and is well known to those skilled in the art (see for example US 2003/0232032 Table 1 pp. 4-24). The spatial orientation and location of each atom in the Cartesian coordinate system is what makes up and

defines three-dimensional protein structures and clearly Table 2 does not disclose this information. Therefore, in the absence of this disclosure, Applicants undoubtedly were not in possession of this aspect of the invention at the time of filing.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

19. Claims 1-3 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sinha et al. (Nature, 2 December 1999, 402:537-540). Sinha et al. teach a peptide inhibitor of beta-secretase (which is a synomym for memapsin 2) where the inhibitor is a P_{10}-P_4, P_1 (*S*)-statine substituted analogue that inhibits the soluble beta-cleavage activity. The claim limitations state a method of treating by administering an inhibitor which has a K_i of 10^{-7} M *or* one which binds to the crystal of mempasin 2. Protein crystals are comprised of 40-60% solvent and possess a huge amount of solvent accessible channels (see Branden and Tooze, p. 270, last paragraph). Thus, a skilled artisan would need only to soak the crystal with a solution containing the inhibitor as taught by Sinha et al. in order to possess an inhibitor that can bind to the crystal of memapsin 2 and one which also inhibits memapsin 2. Thus, the inhibitor as described by Sinha et al. would inherently be capable of treating a patient so as to decrease the likelihood or decrease the

progression of Alzheimer's because these limitations are extremely subjective and the inhibition of even a small amount will be beneficial and will delay the progression. Sinha et al. also recognize that inhibitors of the beta-secretase protein will be vital for treating Alzheimer's (see last paragraph, p. 540).

References of Interest – Not Relied Upon

20. Ghosh et al. (JACS, 2000, 122(3522-3523). Ghosh et al. describe the inhibitors of beta-secretase/memapsin 2 as OM-99-1 and OM-99-2 with K_i values less than 10^{-7} and that these inhibitors would be useful in the treatment of Alzheimer's disease (see p. 3523, column 1, 2nd to last paragraph through to the end of column 2).

21. Chopra et al. (US 2002/0055459 A1) teaches methods of the *in silico* design of inhibitors of beta-site APP cleaving enzyme (BACE, also known as memapsin 2) based on the three-dimensional crystal structure.

22. Tang et al. (US 6,545,127 B1) describes the protein memapsin 2 and crystals thereof.

Conclusion

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber (AU 1653) or Kathleen Kerr (AU 1656) can be reached on 571-272-0925 and 571-272-0931, respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
20 June 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER